Office Action Summary	Application No.	Applicant(s)
	10/560,250	NEMEROW ET AL.
	Examiner	Art Unit
	JOANNE HAMA	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *March 26, 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-68,72 and 80-85* is/are pending in the application.

4a) Of the above claim(s) *59-68 and 72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58 and 80-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☐ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 26, 2010 has been entered.

Claims 1-57, 69-71, 73-79 are cancelled. Claims 59-68, 72 are withdrawn. Claims 58, 80 are amended.

Applicants should note that the instant claims have been examined commensurate with the scope of the elected invention and the species of the invention, i.e. the last repeat of Ad37 (serotype D) and its modified form presented as SEQ ID NO: 48, see species election, February 26, 2008.

Claims 58, 80-85, drawn to an adenovirus particle comprising a modified shaft fiber protein and a modification in the fiber knob to further reduce CAR binding, are under consideration.

It is noted that the Examiner of record has changed.

Maintained Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 58, 80-85 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Vigne et al. US Patent 6,911,199, patented June 28, 2005, previously cited, in view of Hallenbeck et al. US PGPatent Publication 2002/0137213, previously cited, published September 26, 2002, Havenga et al., US PGPatent Publication 2003/0017138, published January 23, 2003, previously cited, Kaleko et al. US PGPatent Publication 2004/0002060, published January 1, 2004, previously cited, for reasons of record, June 11, 2008, January 29, 2009, August 26, 2009.

It is noted that the previous Examiner had indicated the incorrect patent number for Vigne et al.; the number has been corrected above.

The rejection of August 26, 2009 has been consolidated into one rejection, as follows.

Vigne et al. describe targeted adenovirus vectors for delivery of heterologous genes, wherein modifications of the internal sites of the adenovirus fiber protein that include short targeting peptides fused to the C-terminus of the fiber protein, or the fiber HI loop (knob) target the modified adenoparticles to specific cell types (Vigne et al., Title and Abstract). Vigne et al. specifically disclose that the fiber protein can be modified to have a fiber shaft that is shorter than a wild-type fiber shaft, in particular by an in-frame

deletion or by replacing it with the shaft from another serotype (Vigne et al., col. 6, 4th parag.). In Example 3, Vigne et al. teach a shortened Ad5 shaft that retained only 6 or 9 repeats instead of 22 in the native protein (Vigne et al., col. 30), and additionally teach using a SOE35Kg primer corresponding to the last repeat of the Ad3 fiber shaft and primers that include modifications resulting in the creation of restriction sites to generate an intertypic fiber composed of the Ad5 tail, the Ad3 shaft, and part of the Ad5 knob, and flanked with unique restriction sites (Vigne et al., col. 31 and 32, bridging). The disclosed mutation thus encompasses a substitution or replacement of the Ad5 shaft with Ad3, comprising a modification in the last full repeat of the fiber shaft. One mutant adenovirus thus generated (vBS1) was noted to bind less efficiently to CAR (Vigne et al., col. 33). Vigne et al additionally teach that at least a part of the fiber HI loop (knob) is replaced with a ligand peptide or targeting sequence, so as to functionally display its binding specificity at the capsid surface, that may comprise deletion of about 6 to 17 amino acids from the hexon HI loop, preferably not exceeding 11 amino acids (Vigne et al., col. 4). Further teaching: "Capsid modifications that impair the native entry pathway (e.g. fibers displaying short shafts) can therefore be combined with capsid modifications that provide an additional, CAR-independent, pathway of infection." (Vigne et al., col. 47 and 48; bridging).

Vigne et al do not specifically describe the KO1 fiber knob mutation. Hallenbeck et al. describe adenovirus particles mutated in their fiber proteins that no longer bind to their natural cellular receptor and can be retargeted to a specific cell type through the addition of a ligand to the virus capsid (Hallenbeck et al., Abstract). Hallenbeck et al.

specifically described are adenoviral constructs containing the KO1 fiber AB loop mutation (Hallenbeck et al., Fig. 9), displaying a diminished interaction with CAR (Hallenbeck et al., paragraph [0092])), thus providing for the deficiency of KO1 modification in the teachings of Vigne et al., and additionally providing the motivation to introduce the KO1 modification in the fiber knob region. Adenoviral vectors containing the KO1 mutation in conjunction with a ligand targeting moiety are described in Example 3.

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, to combine the teachings of Vigne et al. and Hallenbeck et al. to introduce the KO1 mutation as the fiber knob mutation in a retargeted adenoviral vector, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would have been motivated to introduce the KO1 modification in the fiber knob as taught by Hallenbeck et al., because such mutations would provide an additional CAR-independent pathway of infection for adenovirus retargeting.

With regard to the claims being drawn to the virus having the sequence of SEQ ID NO. 48 (claim 82), Havenga et al. describe chimeric adenoviruses as vectors, wherein the hybrid adenoviruses contain a genome derived from different adenovirus serotypes, displaying a modified host range that overcome the limitations with currently used serotype C adenoviruses (Havenga et al., Abstract). Havenga et al. state: "Preferably, the (chimeric) adenoviruses capable of transducing a CAR negative cell include at least an adenovirus receptor binding part of a fiber protein from an

adenovirus of subgroup D" (Havenga et al., paragraph [0020], further depicting the fiber shaft sequences of type 37 in Fig. 7, and specifically describing Sequence 31, comprising the last full repeat of instantly claimed SEQ ID NO: 48. An artisan would have combined the teachings of Vigne et al., Hallenbeck et al. and Havenga et al. to substitute or modify the last full repeat of the fiber shaft of a serotype 37 in a retargeted adenoviral vector, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would have been motivated to introduce a modification in the fiber shaft as taught by both Vigne et al. and Havenga et al., because such mutations would provide an additional CAR-independent pathway of infection for adenovirus retargeting.

With regard to the claims being drawn to KO12 fiber knob mutation (claims 58, 83, 85). Kaleko et al. describe fiber shaft modifications for efficient targeting of adenoviral vectors that can be combined with other modifications such as fiber knob modifications to produce fully ablated detargeted adenoviral vectors (Kaleko et al., Abstract). Kaleko et al. specifically describe the KO12 modification in paragraph [0040], curing the deficiency in the teachings of Vigne et al., and additionally providing the motivation to introduce the KO12 modification in the fiber knob region. An artisan would have combined the teachings of Vigne et al. and Kaleko et al. to introduce the KO12 mutation as the fiber knob mutation in a retargeted adenoviral vector, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would have been motivated to introduce the KO12 modification in the fiber knob, because such mutations would provide an additional

CAR-independent pathway of infection for adenovirus retargeting, and is specifically taught by Kaleko et al.

Applicant's arguments filed January 26, 2010 have been fully considered but they are not persuasive.

Applicant indicates that according to the Action, Vigne teaches mutations that encompass a substitutions or replacement of the Ad5 shaft with Ad3, thereby comprising a modification in the last full repeat of the fiber shaft. Applicant indicates that amended claim 58 requires an adenoviral particle comprising a modification to a fiber shaft protein, wherein the modification is a mutation, insertion, or replacement of at least one amino acid at contiguous amino acids corresponding to the amino acid sequence set forth in SEQ ID NO. 49 in a fiber shaft beta-repeat corresponding to the last full beta repeat. Applicant indicates that Vigne fails to teach or suggest a modified adenovirus fiber wherein the modification is within SEQ ID NO. 49 in a fiber shaft beta-repeat corresponding to the last full repeat (Applicant's response, pages 5-6). In response, this is not persuasive. As indicated above, Vigne et al. teach using a SOE35Kg primer that corresponds to the last repeat of the Ad3 fiber shaft and primers that include modifications resulting in the creation of restriction sites to generate an intertypic fiber composed of the Ad5 tail, the Ad3 shaft, and part of the Ad5 knob (Vigne et al., cols. 31-32, bridging). The change of an Ad5 to an Ad3 shaft in the last repeat of the Ad3 fiber shaft meet the limitations of the modification being a "mutation, insertion, or replacement of at least one amino acid at contiguous amino acids corresponding to the amino acid sequence set forth in SEQ ID NO. 49" as more than one amino acid

change from an Ad5 sequence to an Ad3 sequence meets the limitation of at least one amino acid mutation, insertion, or replacement. That is, the specification, Figure 2, teaches that SEQ ID NO. 49 is a consensus sequence nested within SEQ ID NOs. 48 and 47 (which are sequences of last full repeats of Ad37 and Ad5) and substitution of the last repeat of Ad5 to that of Ad3 changes at least one amino acid of the consensus sequence SEQ ID NO. 49. Thus, Vigne et al. meet the limitation of the claims.

Applicant indicates that Vigne does not specifically describe the KO1 fiber knob mutation and thus relies upon Hallenbeck for describing the mutation. However, Hallenbeck does not teach or suggest an adenovirus fiber wherein the modification is within SEQ ID NO. 49 (Applicant's response, page 6). In response, this is not persuasive. As indicated above, Vigne et al. meet the limitation of modifying SEQ ID NO. 49.

Applicant indicates with regard to the rejection of Vigne in view of Hallenbeck and Havenga, the Action does not specifically describe the serotype D Ad37 virus having the sequence set forth as SEQ ID NO. 48. The Action relies on Havenga for disclosing that chimeric adenoviruses containing a genome derived in part from an adenovirus of subgroup D. Applicant indicates that even if an artisan would have combined Vigne and Hallenbeck in view of Havenga, the resulting composition would not result in an adenoviral particle comprising a modification of at least one amino acid mutation, insertion, or replacement of at least one amino acid of SEQ ID NO. 49. In response, this is not persuasive. As discussed above, the substitution of the last repeat in the Ad5 shaft with that of Ad3 meet the limitation of the claims. Similarly, Vigne et al. meet the

limitation of claim 82 (modification of SEQ ID NO. 48, the last repeat in Ad37) because the Ad3 sequence in Vigne et al. is a modification in at least one amino acid of SEQ ID NO. 48.

With regard to the rejection of the claims over Vigne and Kaleko, Applicant indicates that Kaleko does not teach or suggest a modified adenovirus fiber wherein the modification is within SEQ ID NO. 49 in a fiber shaft beta-repeat corresponding to the last full beta repeat (Applicant's response, page 7). In response, this is not persuasive. As discussed above, Vigne et al.'s teaching of a substitution of the last repeat of Ad5 with that of Ad3 meet the limitations of the claims.

Thus, the claims remain rejected.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama whose telephone number is 571-272-2911. The examiner can normally be reached Mondays, Wednesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Joanne Hama/
Primary Examiner
Art Unit 1632